REMARKS

The present document is submitted in reply to the office action dated September 15, 2008 ("Office Action").

Applicants have amended claims 1, 7-9, 13, 16, and 17 to promote clarity. Support for the amendments can be found throughout the specification, e.g., at page 4, paragraph [0015]; page 5, paragraph [0018]; page 16, paragraph [0054]; and in Fig. 3. Further, Applicants have amended claims 5 and 13 to correct typographical errors. Finally, they have changed dependency of claims 11 and 12 and cancelled claim 10. Note that claim 2 was cancelled previously. No new matter has been introduced by the proposed amendments.

Upon entry of the present amendments, claims 1, 3-9, and 11-21 will be pending. Among them, claims 4, 7, 9, 15, and 19 have been withdrawn from consideration and claims 1, 3, 5, 6, 8, 9, 11-14, 16-18, 20, and 21 are under examination.

Applicants respectfully request that the Examiner reconsider this application in view of the following remarks.

Claim Objections

The Examiner objects to claims 1, 5, and 13 for containing a punctuation error, a typographical error, and a grammatical error, respectively. See the Office Action, page 3, first paragraph; page 3, second and third paragraphs. Applicants have corrected all these errors.

Non-Statutory Double Patenting

Claims 1, 3, 5, 6, 8, 10-14, 16-18, 20, and 21 are provisionally rejected for non-statutory obviousness-type double patenting over claims 1, 3, 4, 6, and 24-35 of copending Patent Application No. 10/502,190 (the '190 application). See the Office Action, pages 3-5. Applicants respectfully disagree.

Amended claims 1, 3, 5, 6, 8, 11-14, and 16-18 (claim 10 has been cancelled), all method claims, will be addressed first. These claims cover various uses of a signaling

aptamer, including (a) monitoring an enzymatic reaction, (b) detecting an enzyme, (c) quantifying an enzyme, and (d) screening for inhibitors of an enzyme.

Claims 1, 3, 4, 6, and 24-35 of the '190 application cover a signaling aptamer complex. The Examiner correctly points out that this application provides an example of the claimed complex identical to an example of the signaling aptamer required by the rejected claims. See the Office Action, page 4, last paragraph. However, Applicants would like to point out that claims 1, 3, 4, 6, and 24-35 of the '190 application cover a product, i.e., the signaling aptamer complex, and the rejected claims cover processes of using the product.

As set forth in MPEP 806.05(h),

> "A product and a process of using the product can be shown to be **distinct inventions** if either or both of the following can be shown: (A) the process of using as claimed can be practiced with **another materially different product**; or (B) the product as claimed can be used in a **materially different process**;" emphases added.

Here, it is common knowledge that various products can be used in the processes of using as claimed in this application, i.e., (a) monitoring an enzymatic reaction, (b) detecting an enzyme, (c) quantifying an enzyme, and (d) screening for inhibitors of an enzyme. As an example of (a), any molecule (e.g., **antibody**, **peptide**, and **small molecule**) that specifically binds to the substrate or product of an enzyme can be used to monitor the reaction catalyzed by the enzyme. Further, as an example of (b) and (c), **antibody** is commonly used to detect an enzyme or quantify an enzyme. Finally, as an example of (d), any reagent (e.g., **dye-labeled substrate**) indicating the activity of an enzyme can be used to screen for inhibitors of the enzyme. Referring to the above-quoted MPEP 806.05(h), (A) these products (e.g., **antibody**, **peptide**, and **dye-labeled substrate**) are **materially different from** the signaling aptamer complex covered by claims 1, 3, 4, 6, and 24-35 of the '190 application, and (B) the product as claimed in the '190 application, i.e., the signaling aptamer complex, can be used **in materially different processes**, e.g., monitoring an enzymatic reaction (see claim 1 of the present application) and screening for inhibitors of an enzyme (see claim 17 of the present application). Thus,

pursuant to this quoted MPEP guideline, claims 1, 3, 4, 6, and 24-35 of the '190 application, covering a signal aptamer complex, and claims 1, 3, 5, 6, 8, 11-14, and 16-18, covering processes of using the signal aptamer complex, are patentably distinct. Applicants therefore respectfully submit that the rejection of claims 1, 3, 5, 6, 8, 11-14, and 16-18 for obviousness-type double patenting is improper.

Rejected claims 20 and 21, the two product claims in this application, cover kits containing a signaling aptamer, a substrate, and optionally an enzyme that converts the substrate to a product. These two claims require that the signaling aptamer have different affinities to the substrate and to the modified substrate (e.g., the product).

As mentioned above, claims 1, 3, 4, 6, and 24-35 of the '190 application cover a signaling aptamer complex for detecting a target. This complex contains an aptamer oligonucleotide that binds to the target.

According to MPEP § 804,

> "A nonstatutory obviousness-type double patenting rejection is **appropriate** where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is **either anticipated by**, or **would have been obvious over**, the reference claim(s)," citing *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); emphasis added.

In the present case, claims 1, 3, 4, 6, and 24-35 of the '190 application cover an aptamer signaling complex, not a kit of rejected claims 20 and 21, i.e., a kit containing an signaling aptamer, a substrate (of an enzyme) and optionally the enzyme. Clearly, claims 1, 3, 4, 6, and 24-35 of the '190 application do not anticipate the rejected claims. Further, the signaling aptamer complex of claims 1, 3, 4, 6, and 24-35 of the '190 application is used for detecting a target. These claims do not suggest that the target could be a substrate or product of an enzyme. Absent this suggestion, a skilled person in the art would not have been motivated to place the signaling aptamer complex together with an enzyme substrate and further with an enzyme in a container to arrive at the kits of claims

20 and 21. In other words, claims 1, 3, 4, 6, and 24-35 of the '190 application do not render obvious claims 20 and 21 of the present application.

For the foregoing reasons, Applicants submit that claims 20 and 21 are neither anticipated nor obvious over claims 1, 3, 4, 6, and 24-35 of the '190 application. Pursuant to the guideline set forth under MPEP § 804 quoted above, the nonstatutory obviousness-type double patenting rejection of claims 20 and 21 is inappropriate.

In view of the above remarks, Applicants respectfully request that the Examiner withdraw this rejection.

Rejections Under 35 U.S.C. § 102

The Examiner rejects claims 1, 3, 7, 10, 13, and 14 for lack of novelty on two grounds, which will be addressed separately below. See the Office Action, pages 6-8.

I

Claims 1, 3, 7, 10, 13, and 14 are rejected as being anticipated by Gallivan, US Patent Application Publication 2003/0064931 ("Gallivan"). Note that claim 7 have been withdrawn from consideration and claim 10 has been cancelled.

Claim 1 will be discussed first. This claim, as amended, covers a method for monitoring an enzymatic reaction in which an enzyme converts substance A to product B. This method includes (i) mixing substance A with a signaling aptamer that has different binding affinities to substance A and product B to form a mixture, (ii) determining in the mixture a signal released from the signaling aptamer before addition of the enzyme, (iii) adding the enzyme to the mixture, and (iv) determining changes in the intensity of the signal at multiple time points after addition of the enzyme. The signal intensity changes at the multiple time points indicate the conversion levels of the substance A to product B at those time points, i.e., the progress of the enzymatic reaction.

Gallivan teaches a method of cloning a gene of interest using a nucleic acid construct containing an aptamer operably linked to a reporter gene (e.g., a gene encoding a fluorescent protein, or a toxic protein). See Abstract. The aptamer, when binding to a target molecule, controls the expression of the reporter gene in a cell. The product of the

reporter gene releases a readily detectable signal (e.g., fluorescence or cell death). See, e.g., page 7, paragraph [0054].

The method of amended claim 1 differs from the Gallivan method in at least two aspects. First, the former uses a signaling aptamer to monitor an enzymatic reaction in a test tube (i.e., outside a cell) while the latter requires introducing an aptamer into a cell for identifying a gene of interest. As pointed out above, the claimed method requires mixing a substrate of an enzyme (i.e., substance A) with a signaling aptamer to form a mixture and then adding the enzyme to the mixture. In view of these two steps, a skilled person in the art would readily know that this method is performed in a test tube, not inside a cell. Differently, the Gallivan method requires introducing into a cell a nucleic acid construct that includes an aptamer, which controls expression of a reporter gene via binding to a target molecule. Clearly, this method is carried out at the cell level, not outside the cell as required by amended claim 1. Second, the claimed method requires a signaling aptamer, which, according to the specification, is linked with a reporter molecule (for releasing a readily detectable signal). See page 9, paragraph [0041]. By contrast, the aptamer used in the Gallivan method does not release any signal. Rather, the product of the reporter gene, which is operably linked to the aptamer, releases a readily detectable signal. See, e.g., page 7, paragraph [0054].

Given the two differences pointed out above, Applicants submit that amended claim 1 is not anticipated by Gallivan. Nor is claim 3, which depends from claim 1.

Applicants now turn to claims 13 and 14. These two claims, as amended, cover a method of detecting the presence of an enzyme in a test sample. Like amended claim 1, they also require a signaling aptamer, which is not taught in Gallivan. Thus, this claim is also novel over Gallivan.

II

Claims 1, 3, 5, 6, 10, 13, and 14 are rejected as being anticipated by Tyagi et al., Nature Biotechnology 14:303-308 ("Tyagi"). Claim 10 has been cancelled.

As discussed above, amended claims 1 and 13, the two independent claims at issue, both require a signaling aptamer.

Tyagi discloses a molecular beacon for monitoring the progress of polymerase chain reaction, in which a nucleic acid is synthesized. See page 304-305. According to this reference, a molecular beacon is a nucleic acid that forms base-pairs with a target nucleic acid. See Figure 1 at page 304. In other words, the Tyagi beacon is an antisense nucleic acid.

It is commonly known that the term "**aptamer,**" derived from the Latin aptus "to fit," was chosen to emphasize the lock-and-key relationship between an aptamer and its binding partner. See Exhibit 1. Note that base-pairing between two complementary nucleotide sequences, i.e., the interaction between Tyagi beacon and its target nucleic acid, is not a lock-and-key type binding. Thus, a skilled person in the art would not deem the Tyagi beacon as an aptamer. Indeed, as mentioned in the specification, "[a]ptamers are nucleic acids with **ligand-binding capabilities** that are isolated from **random-sequence nucleic acid pools**." See page 1, paragraph [0002]; emphasis added. As the Tyagi beacon is an antisense nucleic acid, a skilled person in the art would readily know that it is particularly designed in view of the target nucleic acid, not isolated from **random-sequence nucleic acid pools**. In short, the Tyagi beacon, an antisense nucleic acid, is not an aptamer as required by claims 1 and 13.

For the foregoing reasons, Applicants submit that claims 1 and 13 are novel over Tyagi. So are claims 3, 5, 6, and 14, which depend from claim 1 or claim 13.

Rejections Under 35 U.S.C. § 103

Claims 1, 3, 5, 6, 8, 10-14, 16-18, 20, and 21 are rejected for obviousness over Tyagi, Gallivan, Jhaveri et al., J. Am. Chem. Soc. 122:2469-2473 ("Jhaveri"), Hamaguchi et al., Anal. Biochem. 294:126-131 ("Hamaguchi"), and Li et al., Biochem. Biophys, Res. Comm. 292:31-40 ("Li"). See the Office Action, pages 9-12. Applicants respectfully disagree.

Applicants discuss amended claim 1 first. As pointed out above, this claim covers a method for monitoring an enzymatic reaction with a signaling aptamer that has different affinities for the substrate of an enzyme and the product of the enzyme. The signaling

aptamer, when binding to the substrate and the product, releases a signal at different intensities, which are indicative of the conversion level of the substrate to the product.

As discussed above, Tyagi discloses use of a molecular beacon, which is an antisense nucleic acid, **not an aptamer**, to monitor an enzymatic reaction. Indeed, to achieve the intended function, the Tyagi molecular beacon must form base pairs to a target nucleic acid. See Figure 1 at page 304. Thus, a skilled person in the art would not have been motivated to replace the Tyagi beacon with an aptamer, which binds to its partner through lock-and-key interaction, not through base-pairing.

As also discussed above, Gallivan discloses a gene cloning method using an aptamer to control reporter gene expression. This reference does not suggest using an aptamer to monitor an enzymatic reaction, the subject matter of amended claim 1. Further, the Gallivan aptamer is very different from the aptamer recited in this claim. Namely, the former **does not release a signal** while the later does. Indeed, as the Gallivan aptamer is used in a cell to control gene expression, which in turn produces a detectable signal. Thus, a skilled artisan would not have been motivated to add a reporter molecule to the Gallican aptamer, thereby arriving at the signaling aptamerr recited in amended claim 1. In short, Gallivan does not suggest the method of amended claim 1, i.e., using a signaling aptamer to monitor an enzymatic reaction based on the intensity of the signal released from the aptamer.

Jhaveri teaches ATP-specific aptamers for use in sensor arrays (see, e.g., page 2469, right column, last paragraph and Fig. 2b). This reference does not suggest use of aptamers for monitoring enzymatic reactions as required by amended claim 1.

Both Hamaguchi and Li disclose molecular aptamer beacons used in direct detection of proteins (see Titles). Note that these aptamers are **specific to proteins**, not to enzyme substrates or enzyme products, as the aptamer recited in amended claim 1. Thus, like the other cited references, these two references also do not suggest using a signaling aptamer specific to an enzyme substrate or to an enzyme product for monitoring an enzymatic reaction.

In sum, none of Tyagi, Gallivan, Jhaveri, Hamaguchi, and Li, either taken alone or in combination, suggests a method for monitoring an enzymatic reaction using a signaling aptamer that releases a signal at different intensities when binding to the substrate of an enzyme and its product. Applicants therefore submit that these cited references do not render amended claim 1 obvious. Nor do they render obvious claims 3, 5, 6, 8, 11, and 12, all of them depend from claim 1.

Next, Applicants discuss claims 13, 16, and 17, all in independent form. These claims cover methods of detecting an enzyme, quantifying an enzyme, and screening for an enzyme inhibitor using the signaling aptamer mentioned above. More specifically, the signaling aptamer used in these methods has different affinities to the substrate and the product of the enzyme and releases a signal at different intensities when binding to the substrate and the product. The intensities of the signal indicate enzyme presence, enzyme activity, or presence of an enzyme inhibitor.

As pointed out above, Tyagi disclose use of an antisense nucleic acid, **not an aptamer**, to monitor an enzymatic reaction; Gallivan teaches use of an aptamer for controlling gene expression, **not for releasing a signal indicative of enzyme presence, enzyme activity, or enzyme inhibitor presence**; Jhaveri suggests anti-ATP aptamers for use in biosensor arrays, **not for use in detecting or quantifying an enzyme, or screening for enzyme inhibitors**; and Hamaguchi and Li teach protein-specific aptamers, **not substrate/product-specific aptamers**.

In view of the above remarks, a skilled person in the art would have understood that none of the five cited references, either taken alone or in combination, suggests the methods of claims 13, 16, and 17 discussed above. Thus, they do not render these three claims obvious. Nor do they render claims 14 and 18 obvious as they depend from and include all limitations of claims 13 and 17, respectively.

Finally, Applicants address claims 20 and 21. These two claims cover kits containing the signaling aptamer described above, a substrate and optionally an enzyme that converts the substrate to a product. The signaling aptamer has different affinities to the substrate and the modified substrate (e.g., the product).

As pointed out above, Tyagi discloses an antisense nucleic acid, not an aptamer. For the aforementioned reasons (see page 11, 4th paragraph), a skilled artisan would not have been motivated to replace the Tyagi antisense nucleic acid with an aptamer. Clearly, this reference does not suggest any aptamer, let along that recited in claims 20 and 21.

Gallivan discloses an aptamer linked to a reporter gene. This aptamer is used for controlling the expression of the reporter gene, not for signaling. In other words, this reference does not suggest the signal-producing aptamer recited in claims 20 and 21.

Jhaveri is concerned about identifying aptamers specific to ATP. See Figure 3 at page 2471. It does not touch on in any way identifying aptamers that have different affinities to ATP and modified ATPs (e.g., ADP and AMP). Thus, this reference also does not suggest the aptamers recited in claims 20 and 21, i.e., having different affinities to a substrate and a modified substrate.[1]

Hamaguchi and Li disclose aptamers that bind to proteins, not aptamers that bind to a substrate of an enzyme and its product with different affinities, as required by claims 20 and 21.

In view of the above remarks, a skilled artisan would have readily known that combining the teachings in the five cited references would not have arrived at the signaling aptamer recited in claims 20 and 21 as discussed above. Thus, these references, either taken alone or in combination, do not render these two claims obvious.

CONCLUSION

It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing

[1] Indeed, this reference does not mention at all any relevance between the aptamers disclosed therein and an enzyme. It clearly does not suggest the kit of claim 21, which contains an enzyme.

in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

The Petition for Extension of Time fee in the amount of $555 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges to Deposit Account No. 50-4189, referencing Attorney Docket No. 77101-005US1.

Respectfully submitted,

Date: 3/16/09

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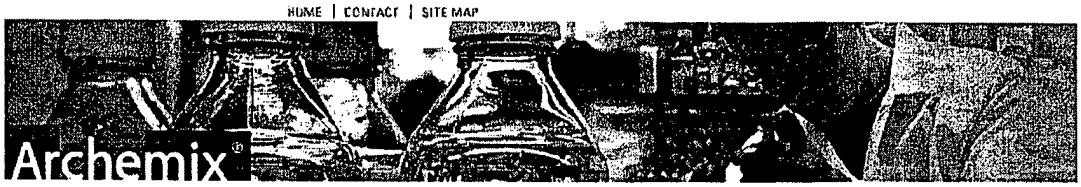
EXHIBIT 1



What is an Aptamer?

Our Science

What is an Aptamer?

Key R & D Functions:

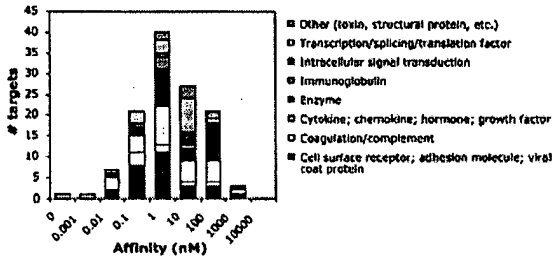
- Aptamer Discovery
- Drug Metabolism & Pharmacokinetics
- Chemistry, Manufacturing, & Controls

Selected Publications

Unlocking the Door to New Therapeutic Solutions

An aptamer is a nucleic acid macromolecule that binds tightly to a specific molecular target. Like all nucleic acids, a particular aptamer may be described by a linear sequence of nucleotides (A, U, T, C and G), typically 15-40 nucleotides long. In solution, the chain of nucleotides forms intramolecular interactions that fold the molecule into a complex three-dimensional shape. The shape of the aptamer allows it to bind tightly against the surface of its target molecule.

The term "aptamer" derives from the Latin aptus, "to fit", and was chosen to emphasize this lock-and-key relationship between aptamers and their binding partners. Because an extraordinary diversity of molecular shapes exist within the universe of all possible nucleotide sequences, aptamers may be obtained for a wide array of molecular targets, including virtually any class of protein, including enzymes, membrane proteins, viral proteins, cytokines and growth factors, and immunoglobulins. The Archemix pipeline includes aptamers directed to a wide range of validated therapeutic targets.



Selectivity and Affinity

Available high-resolution structural data suggests that the surface area of interaction between an aptamer and its molecular target is relatively large, so even small changes in the target molecule can disrupt aptamer association. Thus, aptamers can distinguish between closely related but non-identical members of a protein family, or between different functional or conformational states of the same protein. For example, an aptamer to basic fibroblast growth factor (bFGF) binds with greater than 1,000 fold selectivity to bFGF compared with other members of the FGF family.

Protein	$K_d^{bFGF}/K_d^{protein}$
bFGF (FGF-2)	1.0
denatured	0.0008
FGF-1	0.0003
FGF-4	0.0006
FGF-5	0.041
FGF-6	0.0005
FGF-7	0.0007
VEGF	0.0008
PDGF AB	0.002
AT III	0.000008
thrombin	0.00003

In addition to exhibiting remarkable specificity, aptamers generally bind their targets with very high affinity. A survey of over 150 reported aptamers to a wide variety of targets reveals that the majority of anti-protein aptamers have equilibrium dissociation constants (K_ds) in the picomolar (pM) to low nanomolar (nM) range.